TENT COOPERATION TREATY

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NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:
SCHMITZ, Yvon
Gevers Patents
Holidaystraat 5
B-1831 Diegem
BELGIQUE

23 NOV. 1998

Date of mailing (day/month/year)	
12 November 1998 (12.11.98)	
Applicant's or agent's file reference DPPC 402.012	**IMPORTANT NOTICE**
International application No. PCT/BE98/00064	**International filing date (day/month/year)** 07 May 1998 (07.05.98)
Priority date (day/month/year) 07 May 1997 (07.05.97)	
Applicant PHARLYSE, SOCIETE ANONYME et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CA,CN,EP,IL,JP,KP,KR,NO,PL,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BY,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,GM,GW,HU,ID,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NZ,OA,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   12 November 1998 (12.11.98) under No. WO 98/50016

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

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Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

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If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

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Authorized officer
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NOTIFICATION CONCERNING SUBMISSION OF PRIORITY DOCUMENTS

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year)	
04 June 1998 (04.06.98)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
DPPC 402.012	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/BE98/00064	07 May 1998 (07.05.98)	07 May 1997 (07.05.97)

Applicant

PHARLYSE, SOCIÉTÉ ANONYME et al

The applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to the following application(s):

Priority application No:	Priority date:	Priority country:	Date of receipt of priority document:
97870065.6	07 May 1997 (07.05.97)	EP	29 May 1998 (29.05.98)

The International Bureau of WIPO
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PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
DPPC 402.012		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/BE 98/00064	07/05/1998	07/05/1997
Applicant		
PHARLYSE, SOCI T ANONYME et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
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4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
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   - [ ] as suggested by the applicant.
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   - [X] None of the figures.

XP 002044134

P.D. 1992

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/1 - (C) FILE HCA

AN - 117:239737 HCA

TI - Consolidation and compaction of powder mixtures: III. Binary mixtures of different particle size fractions of different types of crystalline lactose

IN - Riepma, K. A.; Zuurman, K.; Bolhuis, G. K.; De Boer, A. H.; Lerk, C. F.

CS - Dep. Pharm. Technol. Biopharm., Univ. Groningen, Groningen, 9713 AV, Neth.

SO - Int. J. Pharm. (1992), 85(1-3), 121-8
CODEN: IJPHDE; ISSN: 0378-5173

DT - Journal

LA - English

AB - Tablets were compacted from a coarse fraction (250-315 .mu.m), a fine fraction (32-45 .mu.m) and from binary blends of a coarse and a fine fraction of different types of cryst. lactose. The results showed differences in consolidation and compaction between the granular lactose types, i.e., roller-dried .beta.-lactose and anhyd. .alpha.-lactose, and the non-granular lactose types, namely, cryst. .beta.-lactose and .alpha.-lactose monohydrate. Equal particle size fractions of the granular types of lactose exhibited greater specific powder surface areas, less fragmentation on compression, and higher binding capacities than the non-granular types. Slight increases in consolidation were demonstrated on compression of binary blends of the coarse and fine fraction of the different types of lactose. Differences in morphol. between the lactose types were shown by increasing true densities of the granular types when examd. on tablets compacted with increasing compression force. No change in true densities on compaction were demonstrated by the non-granular types.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 98/00064

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 91 11179 A (NATIONAL RESEARCH DEVELOPMENT CORPORATION) 8 August 1991 cited in the application see claims 1-21 ---	1-13
A	WO 95 24889 A (GLAXO GROUP LTD) 21 September 1995 see claims 1-17 see page 4, line 26 - page 5, line 12 ---	1-13
A	US 5 551 489 A (EVA A. C. TROFAST ET AL) 3 September 1996 see the whole document ---	1-13
A	US 3 802 914 A (R. L.NEZBED) 9 April 1974 see the whole document --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
17 August 1998	25/08/1998

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US AN: 117:239737, K. A. RIEPMA ET AL: "Consolidation and compaction of powder mixtures: III. Binary mixtures of different particle size fractions of different types of crystalline lactose" XP002044134 & Int. J. Pharm. (1992), 85(1-3), 121-8 see abstract -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/BE 98/00064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9111179 A	08-08-1991	AU 635616 B	25-03-1993
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/00, 47/26

A1

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(30) Priority Data:
97870065.6 7 May 1997 (07.05.97) EP
(34) Countries for which the regional or international application was filed: BE et al.

(71) Applicant *(for all designated States except US)*: PHARLYSE, SOCIETE ANONYME [LU/LU]; 2, boulevard Royal, L–Luxembourg (LU).

(72) Inventors; and

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(74) Agents: SCHMITZ, Yvon et al.; Gevers Patents, Holidaystraat 5, B–1831 Diegem (BE).

(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

(54) Title: DRY POWDER INHALER EXCIPIENT, PROCESS FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

(57) Abstract

A pharmaceutical excipient useful in the formulation of dry powder inhaler compositions comprising a particulate roller–dried anhydrous β–lactose, said β–lactose particles having a size between 50 and 250 micrometers and a rugosity between 1.9 and 2.4, and the so formulated pharmaceutical compositions.

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Replaced by art. 19 Amendment

CLAIMS

1. A pharmaceutical excipient useful in the formulation of dry powder inhaler compositions, characterized in that it comprises a particulate roller-dried anhydrous β-lactose.

2. An excipient according to claim 1, characterized in that the roller-dried β-lactose particles have a size between 50 and 250 micrometers.

3. An excipient according to claim 2, characterized in that said particles have a size comprised between 100 and 160 micrometers.

4. An excipient according to any of claims 1 to 3, characterized in that said particulate roller-dried anhydrous β-lactose has a rugosity comprised between 1.9 and 2.4.

5. A dry powder inhaler pharmaceutical composition, characterized in that it comprises a mixture of an active ingredient and an excipient as claimed in any one of claims 1 to 4.

6. A composition according to claim 5, characterized in that the active ingredient is a particulate solid with a particle diameter comprised between 0.5 and 6 micrometers.

7. A composition according to either of claims 5 and 6, characterized in that the weight ratio of the active ingredient in relation to the excipient is of from 0.1/100 to 50/100.

8. A composition according to any of claims 5 to 7, characterized in that the active ingredient is selected from the group comprising mucolytics, steroids, sympathomimetics, proteins, peptides and inhibitors of mediator's release.

9. A composition according to claim 8, characterized in that the active ingredient is a mucolytic agent such as L-lysine N-acetylcysteinate.

10. A composition according to claim 9, characterized in that it comprises a mixture of particulate L-lysine N-acetylcysteinate and

roller-dried anhydrous β-lactose constituted by particles of 100 to 160 micrometers in size and of 1.9 to 2.4 in rugosity, the weight ratio of L-lysine N-acetylcysteinate in relation to the roller-dried anhydrous β-lactose being of from 1/2 to 1/6.

11. A composition according to claim 9, characterized in that the weight ratio of L-lysine N-acéthylcysteinate in relation to the roller-dried anhydrous β-lactose is comprised between 1/2 and 1/4.

12. A composition according to claim 11, characterized in that said weight ratio is of the order of 1/4.

13. A process for the preparation of an excipient as claimed in any one of claims 1 to 4, characterized in that anhydrous β-lactose in a powder form is dissolved in demineralised water, fed between two counterrotating drums, which are steam heated and then screeped from the surface of the drums.